

Doxorubicin hydrochloride (liposomal)

Brand Name: Doxil



Drug Description

Doxorubicin is an anthracycline glycoside antineoplastic antibiotic produced by *Streptomyces peucetius* var. *caesius*. [1]

HIV/AIDS-Related Uses

Doxorubicin hydrochloride (HCl) encapsulated in polyethylene glycol (PEG)-stabilized liposomes was approved by the FDA on November 17, 1995, for use as first-line therapy for the treatment of advanced AIDS-related Kaposi's sarcoma (KS) disease that has progressed in spite of prior combination chemotherapy, or in patients who are intolerant of such combination therapy.[2] [3] The conventional, nonencapsulated formulations of the drug have also been used in the palliative treatment of AIDS-related KS.[4]

Non-HIV/AIDS-Related Uses

Liposomal doxorubicin HCl is indicated for the treatment of metastatic ovarian carcinoma that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while the patient is on treatment or within 6 months of completing treatment.[5]

Pharmacology

Doxorubicin is an anthracycline cytostatic antibiotic with activity against a variety of malignancies, including KS. Both in vitro and in vivo, liposomal doxorubicin has been shown to inhibit KS cell growth. Doxorubicin intercalates between DNA strands, inhibiting topoisomerase II activity and inducing tumor cell DNA fragmentation. Additionally, liposomal doxorubicin induces expression of monocyte chemoattractant protein-1, resulting in intralesional recruitment of phagocytic cells in patients with KS. The mechanism by which liposome encapsulation apparently enhances doxorubicin accumulation in AIDS-associated KS is not fully understood, but the passage of liposomal particles through endothelial cell gaps, reported to be present in certain solid tumors and known to be present in KS-like lesions,

may contribute to the enhanced accumulation. Once within the tumor, the active ingredient doxorubicin is presumably released locally as the liposomes degrade and become permeable in situ.[6]

Doxorubicin is extremely irritating to tissues and therefore must be administered by IV. Following IV infusion of a single 10- or 20-mg/m² dose of liposomal doxorubicin HCl in patients with AIDS-related KS, average peak plasma doxorubicin (mostly bound to liposomes) concentrations are 4.33 mcg/ml or 10.1 mcg/ml, respectively, following a 15-minute infusion and 4.12 mcg/ml or 8.34 mcg/ml following a 30-minute infusion. Following IV infusion over 15 minutes of a 40-mg/m² dose of liposomal doxorubicin HCl in AIDS-related KS, peak plasma concentrations averaged 20.1 mcg/ml.[7]

Distribution of liposomal doxorubicin HCl is limited to vascular fluid. During circulation, at least 90% of liposomal doxorubicin remains encapsulated.[8] Encapsulation in PEG-stabilized liposomes substantially slows the rate of distribution into the extravascular space; as a result, the liposomally encapsulated drug distributes mainly in intravascular fluid, whereas nonencapsulated drug distributes widely into the extravascular fluids and tissues. Doxorubicin does not cross the blood-brain barrier or achieve a measurable concentration in cerebrospinal fluid. Trace amounts of doxorubicin have been found in fetal mice whose mothers received the drug during pregnancy, and there is limited data to indicate that nonencapsulated doxorubicin crosses the human placenta. Nonencapsulated drug is distributed into milk, achieving concentrations that often exceed those in plasma; doxorubicinol (the major metabolite) also distributes into milk.[9]

Liposomal doxorubicin HCl is in FDA Pregnancy Category D. Adequate and well-controlled studies have not been done in pregnant women to assess doxorubicin's effects on fertility and pregnancy. Use of the drug is not recommended during pregnancy. Women of childbearing age should be advised to avoid pregnancy during treatment and, in general, use of contraception is recommended during any cytotoxic drug therapy. Studies to

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Pharmacology (cont.)

evaluate the carcinogenic potential of liposomal doxorubicin injection have not been performed; however, the active ingredient doxorubicin is carcinogenic and mutagenic in experimental models. Limited in vitro and in vivo assays have shown that the liposome component of liposomal doxorubicin is not mutagenic.[10]

Protein binding of liposomal doxorubicin has not been determined. Plasma concentrations of liposomally encapsulated doxorubicin HCl appear to decline in a biphasic manner. Following IV administration of a single 10- to 40-mg/m² dose of doxorubicin HCl as a liposomal injection in patients with AIDS-related KS, the initial plasma half-life of doxorubicin averaged 3.76 hours to 5.2 hours, while the terminal elimination half-life averaged 39.1 hours to 55 hours. Plasma clearance of liposomal doxorubicin HCl appears to be substantially slower than that of nonencapsulated doxorubicin.[11]

Adverse Events/Toxicity

Clinical studies of liposomal doxorubicin to treat KS were only performed in patients with AIDS, so assessment of liposomal doxorubicin tolerability was complicated by underlying immune suppression and morbidity commonly present in these patients. Although liposomal doxorubicin was generally well tolerated, there was a strong likelihood that related adverse effects would occur in the majority of the patients. The most common reason for termination of therapy in these studies was death from AIDS-related complications.[12]

Adverse effects associated with liposomal doxorubicin HCl use include anemia, asthenia, fever, infusion reactions, leukopenia, neutropenia, stomatitis, thrombocytopenia, allergic reaction, myocardial toxicity and cardiotoxicity, dyspnea, pain at injection site, palmar-plantar erythrodysesthesia (scaling of skin on hands and feet; reddening, swelling or ulceration of skin), pneumonia, postirradiation erythema recall (darkening or reddening of skin), tachycardia, chest pain, edema, and infection.[13]

Irreversible myocardial toxicity leading to

congestive heart failure, often unresponsive to cardiac supportive therapy, may be encountered as the total dosage of doxorubicin HCl approaches 550 mg/m². Prior use of other anthracyclines or anthracenediones will reduce the total cumulative dose of doxorubicin HCl that can be given without cardiac toxicity. Cardiac toxicity also may occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy. In a clinical trial of 250 patients on cumulative liposomal doxorubicin HCl doses of 450 to 550 mg/m², the risk of cardiac toxicity was 11%.[14]

Acute infusion-related reactions, including flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and hypotension, have occurred in up to 10% of patients treated with liposomal doxorubicin HCl. The initial infusion rate should be 1 mg/min to minimize the risk of infusion reactions.[15]

Doxorubicin HCl should be administered to patients with a history of cardiovascular disease only when the benefit outweighs the risk to the patient. Severe myelosuppression may occur, most commonly as leukopenia in patients with AIDS-related KS. Myelosuppression appears to be dose-limiting at the recommended 20 mg/m² dosage in this population.[16]

Dosage of the infusion should be reduced in patients with impaired hepatic function. The liposomal form should not be substituted for nonencapsulated doxorubicin HCl on a mg per mg basis. Liposomal doxorubicin HCl should be administered only under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.[17]

Drug and Food Interactions

Formal drug interaction studies of PEG-stabilized liposomal doxorubicin have not been performed to date. However, drugs known to interact with nonencapsulated doxorubicin HCl should be considered to interact with the encapsulated liposomal formulation.[18]

Doxorubicin may potentiate the toxicity of other antineoplastic therapies and vice versa. Combined

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Drug and Food Interactions (cont.)

therapy with other myelosuppressive agents may increase the severity of hematologic toxicity. Evidence suggests that concomitant use of cyclosporine and doxorubicin may result in more severe and prolonged hematologic toxicity, and seizures or coma may occur.[19]

Doxorubicin-induced cardiotoxicity may be potentiated by concomitant use of calcium-channel blocking agents. Phenobarbital has increased the elimination of doxorubicin. Doxorubicin has decreased serum phenytoin concentrations. Streptozocin may inhibit hepatic metabolism of doxorubicin.[20]

Contraindications

Liposomal doxorubicin is contraindicated in patients who have a history of hypersensitivity to a conventional formulation of doxorubicin HCl or the components of the liposomal injection. Liposomal doxorubicin is contraindicated in nursing mothers.[21]

Clinical Trials

For information on clinical trials that involve Doxorubicin hydrochloride (liposomal), visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Doxorubicin hydrochloride (liposomal) AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous.[22]

Dosage Form: Doxorubicin HCl (liposomal) for injection at a concentration of 2 mg/ml: in 10-ml sterile, single-use vials each containing the equivalent of 20 mg doxorubicin and in 30-ml sterile, single-use vials each containing the equivalent of 50 mg doxorubicin.[23]

Storage: Unopened vials should be refrigerated at 2 C to 8 C (36 F to 46 F) and protected from freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term (less than 1 month) freezing does not appear to have a

deleterious effect on the drug.[24] When shipped, vials of doxorubicin HCl for injection are packaged with a gel refrigerant ("blue ice") to maintain a temperature of 2 C to 8 C (36 F to 46 F).[25]

Chemistry

CAS Name: 5,12-Naphthacenedione, 10-((3-amino-2,3,6-trideoxy-alpha-L-lyxo-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride, (8S-cis)-[26]

CAS Number: 25316-40-9[27]

Molecular formula: C₂₇H₂₉N-O₁₁.HCl[28]

C_{59.67%}, H_{5.38%}, N_{2.58%}, O_{32.38%} (base)[29]

Molecular weight: 579.99[30]

Melting point: 204 C to 205 C[31]

Physical Description: Orange-red colored thin needles.[32] Translucent, red, liposomal dispersion upon dilution.[33]

Stability: The appropriate dose of liposomal doxorubicin HCl up to 90 mg must be diluted in 250 ml of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 ml of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be observed because no preservative or bacteriostatic agent is present in the formulation. Once diluted, liposomal doxorubicin should be refrigerated at 2 C to 8 C (36 F to 46 F) and administered within 24 hours.[34]

Solubility: Soluble in water, methanol, and aqueous alcohols.[35]

Other Names

Adriablastine[36]

Adriablastin[37]

Adriamycin[38]

Adriblastin[39]

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Other Names (cont.)

Caelyx[40]

Doxorubicin Hydrochloride[41]

Doxorubicina[42]

Liposomal Doxorubicin[43]

Further Reading

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Manufacturer Information

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Doxil
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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